REMARKS

Applicants have carefully studied the Office Action mailed on October 12, 2006, which issued in connection with the above-identified application. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Pending Claims

Claims 18-34 were pending and at issue in the application. Claims 18-34 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and written description. Claims 20 and 21 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 18-25, 28-31 and 34 have been rejected under 35 U.S.C. §103(a) as being obvious over WO 97/44015. Claims 18-25, 28-31 and 34 have been also rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-4 and 13 of the U.S. Patent No. 6,596,318.

Claim 20 has been amended to clarify that that the "granule mixture" is a mixture of (i) granules of particles of the carrier system and (ii) granules of the active ingredient. Claim 21 has been amended to clarify that in the "mixed granules" the carrier system and the active ingredient are both present in one granule particle, i.e., that the mixed granules contain both the biodegradable blood plasma protein and the active ingredient. Support for these amendments can be found, for example, at p. 9, l. 15 - p. 10, l. 3; p. 14, l. 6 - p. 15, l.14; p. 16, l. 33 - p. 17, l. 10. No new matter has been added by these amendments.

Enablement Rejection

In the Office Action, claims 18-34 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner contends that the term "depot" is not enabled because the application does not provide examples or data "that show a delayed or prolonged release of active agent using the medicament formulation claimed."

In response, applicants respectfully note that the Examiner has not provided any reasonable basis for his determination that the claimed composition will not work as a depot and therefore has not satisfied the standard for enablement rejections. As stated in MPEP 2164.04:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)... *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." ...According to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), ... [t]his standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments.

Furthermore, according to the current law and practice, the specification need not contain a specific example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without any undue experimentation. Indeed, as specified in MPEP 2164.02:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed... An applicant need not have actually reduced the invention to practice prior to filing... The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). ...[L]ack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement...

See also *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), where the court stated that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

Applicants further respectfully submit that the present specification enables the claimed depot compositions, because it (i) provides several examples of such claimed compositions (see, e.g., p. 14, l. 6 - p. 17, l. 10); (ii) defines the term "depot" at p. 1, ll. 9-12 (as acknowledged by the Examiner) and p. 4, ll. 25-35; (iii) provides several examples of depot formulations from the prior art (see, e.g., p. 5, ll. 16-37), and (iv) discloses various modes for administration of the claimed compositions (see, e.g., p. 7, ll. 20-35; p. 8, l. 36 - p. 9, l. 10; p. 15, l. 21 - p. 16, l. 26; p. 17, l. 11 - p. 18, l. 6). Based on this disclosure (i-iv), a person of ordinary skill in the art would be confident that the claimed compositions are depot formulations (i.e., mediate a delayed and gradual release of an active ingredient, resulting in its prolonged action) and would be able to demonstrate it by performing routine (not undue) experimentation.

In light of the above practice and arguments, applicants respectfully request withdrawal of the enablement rejection.

Written Description Rejections

In the Office Action, claims 18-34 stand rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. The Examiner contends that the disclosure of the instant specification is not sufficient to support the concept of "depot" medicament formulation, as claimed, and requires further clarification. The Examiner acknowledges that the present specification provides definition of the term "depot" at p. 1, ll. 9-12, where it states that "[r]elease of the active ingredient is intended with the described drug forms to take place in a delayed and gradual manner, resulting in a prolonged action for these drug forms in the sense of a depot." The Examiner asserts, however, that this definition is not clear and concise as applied to the invention being claimed.

In response, applicants respectfully note that the meaning of the term "depot formulation" as provided in the present application is well established in the art and is widely used to refer to formulations being in storage and/or acting over a prolonged period of time (see, e.g., the definition provided in on-line MedPlus Medical Dictionary, attached as Exhibit A). Also, the definition provided at p. 1, ll. 9-12 of the present application is further clarified at p. 4, ll. 27-35, which states that depot drug forms "achieve a delayed or extended release of active ingredient with a slow, constant uptake of active ingredient into the blood stream and thus a constant concentration level of the active ingredient in the blood." In addition, the present specification provides several examples of depot formulations from the prior art (see, e.g., p. 5, ll. 16-37).

The Examiner has also rejected claims 26 and 27 and their dependent claims 32 and 33 for failing to comply with written description requirement. The Examiner contends that the specification does not teach how to make a medicament formulation comprising ceramic granules or calcium phosphate and does not teach how to make a bone replacement implant.

In response, applicants respectfully submit that in the section entitled "Possible formulations may be:" (starting at p. 14, l. 6), the present specification provides a detailed disclosure of how to make a medicament formulation comprising ceramic granules or calcium phosphate and also provides a detailed disclosure of how to make a bone replacement implant. Specifically, as stated at p. 16, ll. 33 - p. 17, l. 10 (emphasis added):

> Porous ceramic granules or granules made of materials for bone replacement, such as, for example, calcium phosphates, which are coated with blood plasma proteins, and these coated granules being compressed to a solid. This solid can then be employed as bone replacement. It is also possible in this case to mix the granules with active ingredients such as antibiotics or growth factors such as, for example, BMP or TGF-β types. One example of BMP is collagen. This can be carried out in such a way that, in a first step, the ceramic granules are coated with a 1st fibrinogen-containing layer. In a 2nd step, thrombin with, for example, growth factors is then applied in a fluidized bed. This can take place as described in DE 198 49 589 C1. The disclosure content is incorporated by reference.

In light of the above arguments, applicants respectfully request withdrawal of the written description rejections.

Indefiniteness Rejections

In the Office Action, claims 20 and 21 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner states that the phrase "granule mixture of particles" in claim 20 is unclear. The Examiner also states that it is unclear whether the term "mixed granules" in claim 21 refers to a mixture comprising (a) granules made of only plasma protein and granules made of only active ingredient, or (b) granules made of both plasma protein and active ingredient.

Claim 20 has been amended to clarify that that the "granule mixture" is a mixture of (i) granules of particles of the carrier system and (ii) granules of the active ingredient.

Claim 21 has been amended to clarify that in the "mixed granules" the carrier system and the active ingredient are both present in one granule particle, i.e., that the mixed granules contain both the biodegradable blood plasma protein and the active ingredient.

Support for these amendments can be found, for example, at p. 9, l. 15 - p. 10, l. 3; p. 14, l. 6 - p. 15, l.14; p. 16, l. 33 - p. 17, l. 10.

In light of these amendments, applicants respectfully request withdrawal of the indefiniteness rejections.

Obviousness Rejection

In the Office Action, claims 18-25, 28-31 and 34 have been rejected under 35 U.S.C. §103(a) as being obvious over WO 97/44015 (Heath et al.). Although the Examiner has withdrawn prior anticipation rejection over this reference, the Examiner states that this reference discloses all limitations of claim 18 (including fluidized bed drying at p. 3, ll. 19-25), except for particle size in the range from 20 to 500 μm. With respect to the latter limitation, the Examiner states that it would have been obvious to one of ordinary skill in the art "to determine suitable particle sizes through routine or manipulative experimentation to obtain the best possible results, as these are variable

parameters attainable within the art." The Examiner further states that the differences in particle size cannot support the patentability of the present invention, unless the applicants can demonstrate "unexpected or unusual results, which accrue from the instant particle sizes." The Examiner concludes that one of ordinary skill in the art would be motivated to make the formulation of the present claims based on the disclosure of WO 97/44015, because WO 97/44015 discloses "good flow properties, enhanced, effective delivery to the active site, and dissolution only at the site."

Applicants respectfully traverse the rejection and note that, in contrast to the Examiner's assertion, WO 97/44015 does **not** disclose fluidized bed drying at p. 3, ll. 19-25. This paragraph as well as the rest of the WO 97/44015 specification discloses only spray drying. Fluidized bed drying recited in the present claims and spray drying disclosed in WO 97/44015 are drastically different processes resulting in particles with drastically different properties. Thus, as stated at p. 3, ll. 9-15 and p. 8, ll. 14-19 of the present application, in contrast to the particles of the present invention produced by fluidized bed drying which are 20-500 μm in size, the spray-dried microparticles disclosed in WO 97/44015 are much smaller in size, generally 1-20 μm, and thus are very prone to dusting and are not free-flowing in practice, which greatly restricts accurate metering and direct application of the solid powder (see also p. 3, ll. 16-18 of WO 97/44015 and sections 6, 11 and 14 of Rule 132 Declaration of Professor Peter C. Schmidt submitted during the prosecution of the U.S. Patent No. 6,596,318, attached as Exhibit B). As specified in sections 7, 11 and 14 and Figure 1 of Dr. Schmidt's Declaration, spray-dried microparticles disclosed in WO 97/44015 are prepared from solution using a pneumatic nozzle which typically produces hollow microspheres which are not free-flowing, difficult to handle (easily crushed), cohesive and cause problems during further processing, transport and storage. In contrast, the larger 20-1000 μm particles produced in a fluidized bed (as are particles of the present application) have a slightly porous granule structure, are compact and are not hollow which makes them dust-free, free-flowing, easily metered, rapidly dissolving, and easy to spread (see sections 8, 10, 12 and 14 and Figures 2 and 3 of Dr. Schmidt's Declaration). Also, in contrast to the fluidized bed technology of the present invention which allows to prepare a mixed product containing both fibrinogen and thrombin granules as well as combination granules containing both proteins, the spray drying method disclosed in WO 97/44015 does not allow the fibrinogen and thrombin to be processed together, as their presence together in a

liquid solution fed to the dryer would cause a premature reaction - forming fibrin before it would be of any use to a patient (see p. 3, ll. 19-20 of WO 97/44015 and sections 5, 7, 9, and 13 of Dr. Schmidt's Declaration).

In sum, by implementing fluidized bed technology, the present invention provides novel means for producing granules that have unexpected advantages over the microparticles of the prior art, particularly of WO 97/44015. The products recited in the present claims 18-25 and 28-31 and the method recited in claim 34 are not an obvious variation of the products and method disclosed in WO 97/44015, due to the differences in particle size, morphology, solubility, dusting and handling properties rendered by the two distinct processes for particle production.

Applicants therefore respectfully submit that the present claims are not obvious over WO 97/44015. Reconsideration and withdrawal of the obviousness rejection is believed to be in order.

Double Patenting Rejections

In the Office Action, claims 18-25, 28-31 and 34 have been also rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-4 and 13 of the U.S. Patent No. 6,596,318 ('318 patent). The Examiner contends that, although the conflicting claims are not identical, they are not patentably distinct from each other, because the '318 patent claims a granulated blood plasma protein medicament formulation produced by fluidized bed drying.

In response, applicants respectfully note that the claims of the present application differ from the claims of the '318 patent in at least two aspects:

(i) while claims of the present application are directed to a biodegradable depot medicament formulation comprising a carrier system and an active ingredient, the claims of the '318 patent are directed to a fibrin tissue adhesive (sealant);

(ii) while claims of the present application encompass formulations comprising both a biodegradable blood plasma protein(s) and an active ingredient, the claims of the '318 patent encompass formulations containing a specific mixture of blood plasma proteins (i.e., thrombin, fibrinogen and factor XIII).

In light of the above, claims 18-25, 28-31 and 34 of the present application and claims 1-4 and 13 of the '318 patent are patentably distinct from each other. It follows, that the non-statutory obviousness-type double patenting rejection should be withdrawn.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 18-34 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

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Respectfully submitted,

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